Specifically, support for the threshold increase in the ability of the dendritic cells to activate prostate antigen specific T cells is found, for example, at page 10, lines 8-12. Support for the dendritic cells being immature as recited in new claim 32 can be found, for example, at page 10, lines 1-7. Activation of either $CD4^+$ and/or $CD8^+$ T cells can be found, for example at page 18, lines 1-9. HLA-matched dendritic cells can be found, for example, at page 10, lines 17-27 and page 18, lines 19-26. All of the amendments presented herein are fully supported by the specification and no new matter has been added to the application. Entry of this amendment is respectfully requested.

Rejections Under 35 U.S.C. § 102:

Claims 23 and 24 remain rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Cohen et al. The Examiner does not consider persuasive Applicants previous argument that the dendritic cells of Cohen are different from those of the invention recited in claims 23 and 24. The Examiner remains convinced that one of skill in the art would have expected that the dendritic cells produced by the methods of Cohen must be fully functional, and could process and present antigen for the following reasons: 1) the dendritic cells produced by the methods of Cohen are fully functional because injection of the cells, which are previously exposed to a prostate tumor lysate, could reduce the size of the prostate tumor in a cancer patient, and 2) it is well known in the art that dendritic cells are antigen presenting cells, therefore, functional dendritic cells would inherently process and present antigens after exposure to the antigens.

Although Applicants believe the dendritic cell compositions of claims 23 and 24 are patentably distinct from those described by Cohen et al. for the reasons previously presented and expanded below, claims 23 and 24 have been amended to further point out the differences between the two compositions. Claim 23 has been amended to clearly set forth that the dendritic cell composition comprises an increased number of human dendritic cells competent and enabled to activate T cells to a prostate antigen than can be directly isolated from peripheral blood. The isolated dendritic cells take up and process the prostate antigen to form prostate antigen activated dendritic cells which can activate T cells, including both $CD4^+$ and $CD8^+$ T

cells. These isolated prostate antigen activated dendritic cells are patentably distinct from the "dendritic cells" of Cohen et al as set forth below. Further, the skilled artisan would not anticipate the presently claimed composition from the disclosure and teachings of Cohen et al., nor would the artisan of ordinary skill anticipate that the activated "dendritic cells" produced by the methods of Cohen would subsequently take up and process antigen to form the dendritic cell composition presently claimed.

Even without amendment to the claims, Applicants must again strongly disagree with the Examiner's conclusions relating to the characteristics of the "dendritic cells" which result from the methods of Cohen. First, the Examiner concludes the "dendritic cells" produced by Cohen are fully functional because injection of the cells, previously exposed to a prostate tumor lysate can reduce the size of the prostate tumor in a cancer patient. This conclusion appears to be based on a prophetic example in the Cohen patent. As Applicants have previously noted this prophetic example is not believed to be based on sound scientific reasoning. The decrease in tumor size identified by the Examiner and suggested by Cohen presupposes that the "dendritic cells" produced by exposure to ionophore can subsequently process and present antigen. Applicants do not believe based on the reasons provided previously and further explained herein below that the skilled artisan could anticipate this result based only on data relating to cell surface phenotype such as that provided by Cohen and a prophetic example.

Second, the Examiner states that dendritic cells are antigen presenting cells and therefore inherently process and present an antigen after exposure to the antigen. As provided previously and discussed further below, dendritic cells only process and present antigen during certain stages of their maturation. The method described by Cohen produces "dendritic cells" which are not in, or have likely passed through, a stage where protein antigen would be processed and presented. At the time the present application was filed Applicants believe the art would suggest that exposure of the "dendritic cells" of Cohen would not process and present antigen.

As previously argued by Applicants there is no evidence that the "dendritic cells" of Cohen can present an antigen to which they were exposed *in vitro* after treatment with ionophore Because of this lack of disclosure one of skill in the art could not anticipate presentation of the new antigen based only on the characterization of the membrane antigen

phenotype of the cells as "dendritic." To support this proposition Applicants provided the Pinkl reference with the previous response. Pinkl demonstrated that cells having a membrane antigen phenotype of a "dendritic cell" without other data, can lack the ability to present antigen.

Applicants now further wish to direct the Examiner's attention to further disclosure in the Cohen patent which are believed would lead a skilled artisan to conclude that the "dendritic cells" of Cohen are unlikely capable of processing and presenting antigen provided *in vitro*. For example, at column 5, lines 31-36 of Cohen the method of the invention is described as "a reliable means to convert the bulk monocyte population to a cellular phenotype indistinguishable from activated dendritic cells" (emphasis added). The Examiner is also directed to column 10, lines 35-38 of Cohen wherein the method is described as useful "for upregulating (activating) dendritic cells and converting monocytes to an activated dendritic cell phenotype" and further that the "method involves our discovery that addition of calcium ionophore to the culture media converts monocytes into activated dendritic cells."

These passages clearly describe the "dendritic cells" of Cohen as activated (or mature) dendritic cells. Therefore, Applicants believe that the skilled artisan would, in fact, anticipate the resultant cells from calcium ionophore treatment would not be able to process any protein antigen. Cohen provides for antigen contacting subsequent to ionophore treatment. The "dendritic cells" one would anticipate might be sufficiently competent to sensitize allogenic T cells because antigen processing and processing subsequent to ionophore treatment is not required. Further, the skilled artisan might also conclude that the cell could be capable of stimulating a limited antibody mediated toxicity directed toward certain antigen sensitized target cells (memory cells), but there would be no anticipation that the activated "dendritic cells" could process and present protein antigen provided subsequent to ionophore treatment.

The inability of the "dendritic cells" of Cohen to process antigen is based on the well known inefficiency of activated (mature) dendritic cells to process and present new antigen. See for example, Koch et al., *J. Immunol.* 155:93-100 (1995)(reference BS) included with the information disclosure statement filed December 1, 1998. In Koch et al. the authors studied the ability of populations of mature and immature dendritic cells to process and present antigen. They determined that populations of "mature" dendritic cells were heterogeneous and included small numbers of immature dendritic cells. Further, they determined that the number

of immature dendritic cells found in a typical population of mature dendritic cells were more than sufficient to produce the level of antigen processing and presentation found in some populations of mature dendritic cells. Koch et al. conclude "[i]n all cases, DC appear to significantly down-regulate their processing capacity upon maturation. There may be circumstances, however, when subsets of residual (partly) immature DC within populations of mature DC endow these populations with biologically significant ability to handle native protein Ag." See, page 99, left column, lines 41-46.

It would appear that even a small number of immature dendritic cells would not be present in the compositions of Cohen because they described their "dendritic cells" as being a homogeneous population of activated or mature "dendritic" cells. For example, at column 10, lines 40-43 provides that "adding the calcium ionophore A23187, for example, at the beginning of a 24-48 hr culture period resulted in uniform activation and dendritic cell phenotypic conversion of the pooled "monocyte plus DC" fractions." Therefore , it is unlikely that this homogeneous population of "activated dendritic cells" would be able to demonstrate an ability to process and present any antigen during an *in vitro* antigen contacting step as proposed by Cohen. Without some explicit disclosure that the method could produce dendritic cells capable of processing and presenting antigen the conclusion of the Examiner would appear to be contrary to a result that would be anticipated by one of skill in the art. Therefore, the Examiner has not provided a proper basis for a rejection under 35 U.S.C. § 102(e).

Further, Applicants provide attached hereto a publication co-authored by Cohen and several other co-inventors of the cited patent published in 1997 which further characterizes the "dendritic cells" disclosed in the Cohen et al. patent. (Czerniecki et al., *J. Immunol.* 159:3823-3837 (1997)). Although this reference published subsequent to the filing date of the present application, the reference is pertinent to the characterization of the "activated dendritic cell" population described in the '786 patent and the ability of the "activated dendritic cell" population to process and present protein antigen. Czerniecki et al. provide a more detailed analysis of the cell surface phenotype of the various subpopulations of cells after elutriation, and prior to and after treatment with ionophore. Populations of both immature dendritic cells and monocytes were identified prior to ionophore treatment (page 3825, right column, third paragraph of the Results section). Treatment with ionophore was characterized by the authors

to "result in rapid, homogeneous conversion of MOMC to a cellular phenotype closely resembling that of spontaneously activated DC." Further, even at the 1997 date of this publication the Cohen lab was still "investigating the ability of CI-treated elutriated MOMC to sensitize autologous T cells rapidly in vitro to a variety of tumor-associated Ag, as well as studying the modulatory effects of cytokines on CI treatment that may promote particular functional outcomes." See page 3836, right column, lines 20-24. It therefore appears that not only the skilled artisan, but even the inventors themselves could not anticipate the "activated dendritic cells" provided by ionophore treatment would necessarily process and present a protein antigen.

Applicants respectfully request the Examiner reconsider and withdraw the rejection of claims 23 and 24 as anticipated by Cohen et al. in light of the above remarks.

Rejections Under 35 U.S.C. § 103

Claim 26 remains rejected under 35 U.S.C. § 103 as allegedly obvious over Cohen et al. in view of Lutz et al. because the Examiner believes that Cohen et al. disclose isolated dendritic cells which have been exposed to prostate tumor lysates and that Lutz et al. disclose making immortalized dendritic cells.

Applicants must again traverse this rejection. As above Cohen et al. do not disclose the presently claimed isolated prostate antigen activated human dendritic cell compositions. Therefore, Lutz et al. add nothing to render obvious modified dendritic cells, *i.e.*, expanded life span or immortalized dendritic cells, which have been presented and process prostate antigen *in vitro*. It is respectfully requested that the Examiner reconsider and withdraw the rejection of claim 26 under 35 U.S.C. § 103 as obvious over Cohen et al. in view of Lutz et al. in light of the above amendments and remarks.

Claims 28 and 29 remain rejected under 35 U.S.C. § 103 as allegedly obvious over Cohen et al. in view of Taylor et al. because the Examiner believes that it would have been obvious to use the cryopreservation techniques of Taylor et al. to preserve the dendritic cells of Cohen et al. Further, the Examiner believes that one of ordinary skill in the art would have

expected that the dendritic cells would have remained functional dendritic cells after cryopreservation.

Applicant must again traverse this rejection. The Examiner as above, believes that the dendritic cells of Cohen are the same as the dendritic cells of the present invention. As demonstrated above, the dendritic cells compositions of the present invention are patentably distinct from those disclosed by Cohen et al. As the compositions comprising the dendritic cells are patentably distinct the compositions of claim 28 and 29 are also patentably distinct. There can be no suggestion to combine the references as suggested by the Examiner. Further, *In re Kerkhoven* is not on point because the two alleged compositions combined to form a third composition of the present claims are not both disclosed in the prior art. It is respectfully requested that the Examiner reconsider and withdraw the rejection of claims 28 and 29 under 35 U.S.C. § 103 as obvious over Cohen et al. in view of Taylor et al. in light of the above amendments and remarks.

Claim 30 remains rejected under 35 U.S.C. § 103 as obvious over Cohen et al. in view of Taylor , further in view of Lutz et al. believing the motivation for to use the immortalization techniques as taught by Lutz et al. to immortalize dendritic cells taught by Cohen et al., which have been cryopreserved by the techniques of Taylor et al. follows from logical reasoning. In particular, it would have been obvious to cryopreserve dendritic cells so that one could use dendritic cells any time in the future without having to maintain a fresh culture of dendritic cells.

Applicants as above, must again transverse this rejection. The logic of the Examiner's rejection requires that the claimed dendritic cells of the present invention are the same as the dendritic cells disclosed by Cohen et al. Without Cohen et al. none of the other references disclose or suggest the presently claimed invention. As Cohen et al. do not disclose or suggest the claimed dendritic cells immortalization of the cells of Cohen and cryopreservation of those cell can not disclose of suggest the composition of claim 30. Again Applicants believe the Examiner has failed to make out a *prima facie* case of obviousness. Applicants therefore respectfully request the Examiner reconsider and withdraw the rejection of claim 30.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 21 December 2000

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